REMARKS/ARGUMENTS

Claims 119-123 are pending in this application and are rejected on various grounds. The rejections to the presently pending claims are respectfully traversed.

Claim Rejections – 35 U.S.C. §§101 and 112, First Paragraph

Claims 119-123 remain rejected under 35 U.S.C. §101 allegedly "because the claimed invention lacks a credible, specific and substantial asserted utility or a well established utility."

Claims 119-123 remain further rejected under 35 U.S.C. §112, first paragraph, allegedly "since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility, one skilled in the art would not know how to use the claimed invention."

The Examiner maintains this rejection indicating that "the specification provides data showing a very small increase in DNA copy number- about 2.5 fold- in many types of normal and cancerous tissue, not just one kind of cancer (see table 8)...there is no evidence regarding whether or not PRO1153 mRNA or polypeptide levels are reliably increase in a cancer." The Examiner maintains this rejection based on the teachings of Pennica *et al.*, Haynes *et al.* and Hu *et al.* Regarding the Hu *et al.* reference, the Examiner specifically says that "it is difficult to fault "bias in the literature" in the Hu article when the study simply aimed to compare the message with protein for 2286 genes in breast cancer....a discussion, by the authors of the possible sources of error in an extensive survey is not unusual in a well-crafted research paper." The Examiner adds, "(r)egardless of whether there is a correlation between mRNA or DNA amplification and protein levels in a sample, the data presented in the instant application do not show a consistent positive response even among the cancer samples." Applicants respectfully disagree and traverse this rejection.

Applicants maintain that the specification, as filed, provides sufficient disclosure to establish a specific, substantial and credible utility for the PRO1153 polypeptide of SEQ ID NO:351 and antibodies thereof and that the increase in amplification is not small. In fact, Applicants submit a Declaration by Dr. Goddard that explains that a gene identified as being amplified at least 2-fold by the disclosed gene amplification assay in a tumor sample relative to a normal sample is useful as a marker for the diagnosis of cancer, and for monitoring cancer

development and/or for measuring the efficacy of cancer therapy. This Declaration provides a statement by an expert in the relevant art stating that " fold amplification" values of at least 2-fold are considered significant in the TaqMan™ PCR gene amplification assay. Applicants particularly draw the Examiner's attention to page 3 of the Goddard Declaration which clearly states that:

> It is further my considered scientific opinion that an at least **2-fold increase** in gene copy number in a tumor tissue sample relative to a normal (*i.e.*, non-tumor) sample is significant and useful in that the detected increase in gene copy number in the tumor sample relative to the normal sample serves as a basis for using relative gene copy number as quantitated by the TaqMan PCR technique as a diagnostic marker for the presence or absence of tumor in a tissue sample of unknown pathology. Accordingly, a gene identified as being amplified at least 2-fold by the quantitative TaqMan PCR assay in a tumor sample relative to a normal sample is **useful as a marker for the diagnosis of cancer**, for monitoring cancer development and/or for measuring the efficacy of cancer therapy. (Emphasis added).

Accordingly, the **2.014 to 2.87**-fold in two different lung primary tumors would be considered significant and credible by one skilled in the art, based upon the facts disclosed in the Goddard Declaration.

Further Applicants submit that the fact that two lung tumor samples tested positive in this study does not make the gene amplification data, by any means, less significant or spurious. As any skilled artisan in the field of oncology would easily appreciate, not all tumor markers are generally associated with every tumor, or even, with most tumors. In fact, some tumor markers are useful for identifying rare malignancies. That is, the association of the tumor marker with a particular type of tumor lesion may be rare, or, the occurrence of that particular kind of tumor lesion itself may be rare. In either event, even these rare tumor markers, which may not give a positive hit with most common tumors, have great value in tumor diagnosis, and consequently, in tumor prognosis. The skilled artisan would know that such tumor markers are very useful for better classification of tumors. Therefore, whether the PRO1153 gene is amplified in two lung tumors or in most lung tumors is not relevant to its identification as a tumor marker, or its patentable utility. Rather, whether the amplification data for PRO1153 is significant is what lends support to its usefulness as a tumor marker. It was well known in the art at the time of

filing of the application that gene amplification, which occurs in most solid tumors like lung cancers, is generally associated with poor prognosis. Therefore, the PRO1153 gene becomes an important diagnostic marker to identify such malignant lung cancers, even if the malignancy associated with PRO1153 molecule is a rare occurrence. Therefore, the gene amplification levels of **2.014 to 2.87**-fold for lung primary tumors is not a "small increase" as the Examiner contends. Applicants also submit that, as any skilled artisan in the field of oncology would easily appreciate, not all tumor markers are generally associated with every tumor, or even with most tumors. Therefore, whether the PRO1153 gene is amplified in few tumor samples or in the vast majority of tumor samples studied is not relevant to its identification as a tumor marker, or its patentable utility. Rather, the fact that the amplification data for PRO1153 is considered significant is what lends support to its usefulness as a tumor marker.

As discussed previously, it is not a legal requirement to establish a "necessary" correlation between an increase in the copy number of the mRNA and protein expression levels that would correlate to the disease state or that it is "imperative" to find evidence that protein levels can be accurately predicted. As discussed above, the evidentiary standard to be used throughout *ex parte* examination of a patent application is a preponderance of the totality of the evidence under consideration. Accordingly, the question is not, as the Examiner suggests, whether a necessary or even "strong" correlation between an increase in copy number and protein expression levels exists, rather if it is more likely than not that a person of ordinary skill in the pertinent art would recognize such a positive correlation. Applicants respectfully submit that when the proper evidentiary standard is applied, a correlation must be acknowledged.

Applicants further maintain, for the reasons provided in the previous response that Pennica *et al.* and Haynes do not show that a lack of correlation between gene (DNA) amplification and elevated mRNA levels, in general, exists. Also, as indicated in the previous response, according to the authors themselves, the Haynes data confirm that there is a general trend between protein expression and transcript levels, which meets the "more likely than not standard" and shows that a positive correlation exists between mRNA and protein. Applicants submit that the Examiner's reasoning is based on a misrepresentation of the scientific data presented in Haynes *et al*, and application of an improper, heightened legal standard.

Applicants also presented reasons why the art considers that, if a gene is amplified in cancer, it is more likely than not that the encoded protein will be expressed at an elevated level. Applicants discussed three articles, Orntoft, Hyman and Pollack *et al.* Applicants also presented two Declarations by Dr. Polakis and Dr. Ashkenazi. Taken together, the data presented in these three papers, Haynes *et al.* and the Declarations clearly showed that "*it is more likely than not*" that a gene which is amplified in tumor cells will "most likely" also have increased gene expression. Therefore, a utility for the PRO1153 protein and its antibodies thereof in the diagnosis of cancer has also been asserted.

Regarding the Hu *et al.* reference, Applicants had submitted that Hu's conclusion only applies to a specific type of breast tumor (estrogen receptor (ER)-positive breast tumor) and **can not be generalized as a principle governing microarray study of breast cancer in general**, let alone the various other types of cancer genes in general. In fact, even Hu *et al* admit that ., "[i]t is likely that this threshold will change depending on the disease as well as the experiment. Interestingly, the observed correlation was only found among ER-positive (breast) tumors not ER-negative tumors." (See page 412, left column). Therefore, while Hu *et al.* compared several breast cancer samples, Applicants submit that their conclusions apply to a specific type of breast tumor (estrogen receptor (ER)-positive breast tumors) and cannot be generalized as a principle governing microarray study of breast cancer in general, let alone the various other types of cancer genes in general.

Therefore, Applicants request that the Examiner reconsider this rejection and maintain that they have demonstrated utility for the PRO1153 polypeptide and antibodies thereof as diagnostic markers for human lung tumors. Accordingly, the present 35 U.S.C. §101 and §112, first paragraph, utility rejections should be withdrawn.

The present application is believed to be in *prima facie* condition for allowance, and an early action to that effect is respectfully solicited.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. **08-1641** (referencing Attorney's Docket No. **39780-2730 P1C32**).

Please direct any calls in connection with this application to the undersigned at the number provided below.

Respectfully submitted,

Date: October 27, 2005

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